PREVALENCE OF ABNORMAL LIVER FUNCTION TEST IN TYPE II DIABETES MELLITUS

submitted to
The Tamil Nadu Dr.M.G.R.Medical University

M.D. DEGREE EXAMINATION
BRANCH – I (GENERAL MEDICINE)

Kilpauk Medical College

Chennai

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

CHENNAI

APRIL 2011

ACKNOWLEDGEMENT

I humbly submit this work to the **Almighty** who has given the health and ability to pass through all the difficulties in the compilation and proclamation of this blue print.

I wish to express my sincere thanks to our Dean, **Dr.V.KANAGASABAI, M.D.,** for permitting me to use the resources of this institution for my study.

I owe special thanks to Superintendent **Prof. Dr. K. THIYAGARAJAN, M.S.M.C.H., DNB (URO),** and Deputy Superintendent **Prof. Dr. N. GUNASEKARAN, M.D., DTCD., GOVT. ROYAPETTAH HOSPITAL,** for permitting me to use the resources .

I feel indebted to **Prof. Dr. G. RAJENDRAN, M.D.,** Head of the Department, Department of General Medicine, for his constant encouragement, innovative ideas, and timely suggestions during my work.

I owe special thanks to my Unit Chief, **Prof. Dr.K.T.JAYAKUMAR, M.D.,** Department of General medicine, for his constant support, invaluable suggestions, erudite guidance in my study and for being a source of inspiration in my endeavours.

My sincere thanks to **Prof. Dr. N. RAGHU, M.D.,** Kilpauk medical college, Chennai, for his valuable guidance and support throughout my study.

I also express my sincere thanks to our Assistant Professors, **Dr. SHAIK SULAIMAN MEERAN, M.D., Dr.K.E.GOVINDARAJULU M.D., Dr.S.SWARNALATHA, M.D.,** for their support in my study.

I would like to thank all my colleagues and all staffs of Department of General medicine, Govt. Royapettah hospital, Chennai for their help and encouragement.

I would like to thank the Institutional Ethical committee for approving the study.

Finally I am indebted to my parents and my husband who have been solid pillars of everlasting support and encouragement and for their heartfelt blessings.

INDEX

Sl.No.	TITLE	PAGE NO.
I	INTRODUCTION	1
II	AIM OF THE STUDY	3
III	REVIEW OF LITERATURE	4
IV	MATERIALS AND METHODS	32
V	RESULTS	36
VI	DISCUSSION	46
VII	SUMMARY	53
VIII	CONCLUSION	55
IX.	ANNEXURES	
	BIBLIOGRAPHY	
	PROFORMA	
	ABBREVIATIONS	
	MASTER SHEET	

INTRODUCTION

Diabetes mellitus is a complex metabolic condition defined by level of hyperglycemia giving rise to micro vascular and macro vascular complications[1].Current estimates suggests that there are 170 million people suffering from DM world wide and this number is going upto 266 million by 2030[2].The prevalence of DM in India is around 31 million and this number will increase to 80 million by 2030[2]. Indians develop diabetes at younger age, with lower degree of obesity and have increased risk of chronic diabetic complications.Hence DM is a major public concern in India.Various complications related to micro or macro vascular diseases like retinopathy,nephropathy, neuropathy,ischemic heart diseases and peripheral vascular disease have been reported. Liver diseases is often overlooked as a complication of DM.

Infact VERONA-DIABETES POPULATION BASED STUDY has shown that among patients with DM standardised mortality rate from cirrhosis was higher than cardiovascular diseases[3].Though association of diabetes with cirrhosis has been recognised for more than 100 yrs, liver diseases in diabetes remains under estimated[4].

Abnormal liver function test results are more common in diabetes mellitus than in the non diabetic population as well as in patients with type 2

diabetes than in those with type 1 diabetes. Elevated activities of the two serum transaminases; alanine transaminase (ALT) and aspartate transaminase (AST) may be associated with liver disease. Elevation of these enzymes is strongly related to obesity, diabetes and dyslipidemia, and their measurement may act as a surrogate marker of NAFLD presence.

This study was conducted to estimate the prevalence of elevated liver transaminase levels among patients with type 2 diabetes and to determine the associated risk factors.

AIM OF THE STUDY

The aim of this study was to determine prevalence of abnormal liver function test in patients with type 2 diabetes and to determine associated risk factors.

REVIEW OF LITERATURE

Diabetes mellitus is known to be associated with a number of liver disorders including isolated elevation of liver enzyme levels, nonalcoholic fatty liver disease (NAFLD), and other chronic liver disorders like hepatitis C infection (HCV), cirrhosis and hepatocellular carcinoma[3,5,6]. Abnormal liver function test results are more common in diabetes mellitus than in the non diabetic population as well as in patients with type 2 diabetes than in those with type 1 diabetes. Elevated activities of the two serum transaminases; alanine transaminase (ALT) and aspartate transaminase (AST) may be associated with liver disease. Elevation of these enzymes is strongly related to obesity, diabetes and dyslipidemia, and their measurement may act as a surrogate marker of NAFLD presence.[3,7] Of the two enzymes, ALT appears to have a role in gluconeogenesis,[8] and seems to be more related to liver fat accumulation than AST.[9] Some authors have suggested that minor elevation of this enzyme's level may be a good predictor of mortality from liver disease.[10] A study of the association of serum ALT activity and ten-years' risk of cardiovascular disease in participants of the Third National Health and Nutrition Examination Survey (NHANES- III) had reported that those with elevated ALT levels had a higher calculated cardiovascular disease risk than those with normal ALT

activity, if viral hepatitis or excessive alcohol consumption were excluded. [11]

The activity of ALT in the hepatocytes is 7000 fold greater than in the serum, [12] and this abundance is the reason for using it as a marker for NAFLD in many epidemiological studies. Clark et al.[13] proposed that elevated AST or ALT levels are predictive of the presence of NAFLD if two basic criteria are met: 1) exclusion of alternative chronic liver diseases, e.g. alcoholic liver disease, hepatitis B or C infection, and hemochromatosis; and 2) presence of features of the metabolic syndrome.

SPECTRUM OF LIVER DISEASES IN DIABETES:

ESTABLISHED	**PROPOSED**
NAFLD NASH NASH WITH CIRRRHOSIS CRYPTOGENIC CIRRHOSIS HEPATOCELLULAR CARCINOMA	GLYCOGENIC HEPATOPATHY DIABETIC HEPATOSCLEROSIS

DIABETES AND LIVER DISEASE:

1. Liver diseases causes diabetes

2. Diabetes contributes to or cause liver diseases

3. Risk factor for liver disease and diabetes are same e.g.alcoholic liver disease with alcoholic chronic pancreatitis.

IMPACT OF DIABETES ON LIVER DISEASE:

CONDITION	INCIDENCE	LEVEL OF EVIDENCE
ACUTE LIVER FAILURE	INCREASED	3a
CHRONIC LIVER DISEASES	INCREASED	2a
CIRRHOSIS	INCREASED	2a
HEPATOCELLULAR CARCINOMA	INCREASED	1a
MORTALITY DUE TO LIVER DISEASES	INCREASED	2a

DIABETES DUE TO LIVER DISEASES:

Cirrhosis is associated with impaired glucose tolerance in more than 80% of patients[19] .Overt diabetes is seen around 20% of cirrhotics. Pathogenesis of diabetes and cirrhosis include peripheral and hepatic insulin resistance and decreased beta cell function.Increased mortality and increased risk of HCC has been shown in patients who develop diabetes.[20]

THEORIES BEHIND LFT ELEVATION IN DIABETES:

The liver helps maintain normal blood glucose concentration in the fasting and postprandial states. Loss of insulin effect on the liver leads to glycogenolysis and an increase in hepatic glucose production. Abnormalities of triglyceride storage and lipolysis in insulin-sensitive tissues such as the liver are an early manifestation of conditions characterized by insulin resistance and are detectable earlier than fasting hyperglycemia. The precise genetic, environmental, and metabolic factors and sequence of events that lead to the underlying insulin resistance, however, is not fully understood.[14]

In animal models, chronic hyperinsulinemia is found to predispose the liver to relative resistance to insulin. This is characterized by a failure of insulin to signal an increase in insulin receptor substrate-2. Upregulation of sterol regulatory element-binding protein 1c (SREBP-1c) also occurs, leading to increased lipogenesis.[15] Despite down-regulation of the insulin receptor substrate-2-mediated insulin signaling pathway in insulin-resistant states, the up-regulation of SREBP-1c and subsequent simulation of de novo lipogenesis in the liver leads to increased intracellular availability of triglycerides, promoting fatty liver. This also increases VLDL assembly and secretion.[14] Thus, hyperinsulinemia might directly lead to hepatic insulin resistance with associated fatty changes.

The excess in free fatty acids found in the insulin-resistant state is known to be directly toxic to hepatocytes. Putative mechanisms include cell membrane disruption at high concentration, mitochondrial dysfunction, toxin formation, and activation and inhibition of key steps in the regulation of metabolism.[16] Other potential explanations for elevated transaminases in insulin-resistant states include oxidant stress from reactive lipid peroxidation, peroxisomal beta-oxidation, and recruited inflammatory cells. The insulin-resistant state is also characterized by an increase in proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), which may also contribute to hepatocellular injury. In preliminary studies, an increased frequency of specific TNF-α-promoter polymorphism was found in nonalcoholic steatohepatitis (NASH) patients, suggesting a possible genetic link or predisposition to fatty liver found in insulin-resistant states.[17]

The above theories all attribute elevated transaminases to direct hepatocyte injury. It is also hypothesized that elevation in ALT, a gluconeogenic enzyme whose gene transcription is suppressed by insulin, could indicate an impairment in insulin signaling rather than purely hepatocyte injury[18].

NON ALCOHOLIC FATTY LIVER DISEASE

NAFLD is the most common etiology of chronically elevated LFTs in the United States in both diabetic and nondiabetic individuals.[17] The estimated prevalence of aminotransferase elevations in the general population from the third National Health and Nutrition Examination Survey data is 7.9%, with about two-thirds of cases unexplained. Of the unexplained cases, most are strongly associated with metabolic syndrome and probably represent underlying NAFLD.

Currently NASH is considered to be hepatic manifestation of metabolic syndrome.[21] Patients with NAFLD have an increased risk of cardiovascular and liver morbidity.[22-23]Diabetic patients with NAFLD are at increased risk of advanced liver diseases, cirrhosis and HCC. NAFLD is an important cause of cryptogenic cirrhosis.[17-26]

NAFLD is a clinicopathological condition representing a spectrum of histological findings from simple hepatic steatosis or steatosis with mild inflammation(type 1 & 2), to hepatic steatosis with a necroinflammatory component that may or may not have fibrosis, or NASH(type 3 & 4). Type 1 & 2 infrequently progress to cirrhosis, whereas type 3 & 4 progress to cirrhosis in 15 -30 % of patients.NAFLD has become a common cause of liver transplant in US.It has also been associated identified as an important

risk factor for development of primary liver cancer mostly due to NAFLD associated cirrhosis.

DEFINITION AND TERMS:

NON ALCOHOLIC FATTY LIVER DISEASES:

Presence of fatty infiltration of liver as exceeding 5 % weight and frequently taken as fat in >5—10% of macrosteatotic hepatocyte in biopsy specimen.

PRIMARY NASH:

The term is occasionally encountered in literature but not widely accepted. It indicates NASH associated with central obesity and often type 2 diabetes, but without a specific, additional etiological factors.

SECONDARY NASH:

NASH associated with a specific problem such as effect of a drug or bariatric surgery.

PRESUMED NASH or NAFLD:

In several epidemiological and pediatric studies, NASH has been used as presumptive diagnosis because of abnormal liver enzyme levels, negative

results of viral studies and echogenic or bright liver at USG consistent with fatty infiltration.

PATHOGENESIS OF NAFLD

The most-recognized proposal for the pathogenesis of NASH is a "two-hit" hypothesis.[24] Hepatic fat accumulation in the liver due to insulin resistance and subsequent hyperinsulinemia represents the "first hit," which induces a "second hit" including oxidative stress, and increased cytokine release. These modifications enhance lipid peroxidation, hepatocyte injury, and release of toxic byproducts, resulting in necroinflammation and fibrosis.

Another important pathogenic culprit is adipocytokines secreted by the white adipose tissue (WAT) related to visceral obesity. White adipose tissue is now recognized as an endocrine organ that secretes several adipokines and cytokines including adiponectin, leptin, resistin, and visfatin, TNF-α, interleukin-6 and angiotensinogen.[25] Adiponectin is an adipokine that is decreased in obesity. Furthermore, plasma adiponectin levels are decreased in NAFLD, whereas exogenous adiponectin improves hepatic steatosis in animal models of non-alcoholic fatty liver.[25] The pro-inflammatory cytokine, TNF-α, is increased in NAFLD patients and therapy directed against it can be beneficial.[26] There is evidence that leptin modulates insulin secretion and insulin activity, but insulin on the other

hand can also regulate leptin expression. Liver, skeletal muscle and adipocytes express leptin receptors. Although leptin increases insulin sensitivity in rats, it increased hepatic insulin resistance in humans by decreasing phosphorylation of insulin receptor substrate. Moreover, serum leptin levels correlated with steatosis in patients with NASH but do not correlate with hepatic fibrosis in humans. Resistin is a recently identified adipokine causing insulin resistance.[27]

Further studies are needed to define the pathogenesis of NAFLD clearly and explain the apparent interindividual variation in the susceptibility to progress to more-advanced liver disease. Genetic factors have been suggested to play an important role in this variation, and several new candidate genes have been proposed.

CONDITIONS ASSOCIATED WITH NON ALCOHOLIC FATTY LIVER

Insulin resistance

a. Syndrome X
    - Obesity
    - Diabetes
    - Hypertriglyceridemia
    - Hypertension

b. Lipoatrophy

c. Mauriac syndrome

Disorders of lipid metabolism

a. Abetalipoproteinemia
b. Hypobetalipoproteinemia
c. Andersen's disease
d. Weber-Christian syndrome

Total parenteral nutrition

Bariatric surgery

a**.**jejuno ileal bypass

b.gastric bypass or gastroplasty

Iatrogenic

a. Amiodarone
b. Diltiazem
c. Tamoxifen
d. Steroids
e. Highly active antiretroviral therapy
f. **Refeeding syndrome**

Toxic exposure(carbontetrachloride,perchloroethylene,phosphorus, ethyl bromide)

SIGNS AND SYMPTOMS:

The signs and symptoms of nonalcoholic fatty liver disease (NAFLD) vary widely, depending on the stage of the condition.The majority of individuals with NAFLD have no symptoms and a normal examination. Children may exhibit symptoms such as abdominal pain, which may be in the center or the right upper part of the abdomen, and sometimes fatigue. However, other causes of abdominal pain and fatigue should be considered. On physical examination the liver might be slightly enlarged and some children may have patchy, dark discoloration of the skin present (acanthosis nigricans) most commonly over the neck and the under arm area... However, as the disease advances, patients may experience symptoms of cirrhosis.

LABORATORY FINDINGS:

In a patient with suspected NAFLD or NASH, useful baseline testing should include levels of AST, ALT, total and direct bilirubin, and fasting serum glucose, as well as a lipid panel. Mild to moderate elevation of serum aminotransferase levels is most commonly found (mean range, 100-200 IU/L). Generally, the ratio of AST to ALT is less than 1, but this ratio increases as fibrosis advances. Liver enzyme levels are normal in a large percentage of patients with NAFLD; normal aminotransaminase levels do

not exclude the presence of advanced disease. Serum alkaline phosphatase and γ-glutamyl transpeptidase levels may also be mildly abnormal.

Given that more than 80% of patients with NAFLD have some components of the metabolic syndrome, serum levels of fasting cholesterol and triglycerides, as well as fasting glucose and insulin, should be determined. Albumin, bilirubin, and platelet levels are usually normal unless the disease has evolved to cirrhosis. There is elevation of serum IgA and lowering of serum IgG/IgA.Some patients with NAFLD have low titers of autoimmune antibodies (antinuclear and anti–smooth muscle antibody) and an elevation of ferritin. The role of these markers is still unclear.

IMAGING:

A liver ultrasound examination is useful for confirming steatosis. Fatty infiltration of the liver produces a diffuse increase in echogenicity and vascular blurring. Unfortunately, ultrasound cannot rule out steatohepatitis or fibrosis, and its sensitivity drops sharply when less than 30% of hepatocytes contain fat droplets.

Both computed tomography (CT) and magnetic resonance imaging (MRI) studies, especially the new technique of magnetic resonance spectroscopy, are more sensitive modalities for quantifying steatosis. However, none of these imaging techniques has sufficient sensitivity and

specificity for staging the disease and cannot distinguish between simple bland steatosis and NASH with or without fibrosis.

LIVER BIOPSY:

Liver biopsy is of unquestioned value in determining the presence of steatosis, distinguishing steatosis from steatohepatitis, and assessing the degree of fibrosis. Because the diagnostic accuracy of noninvasive diagnostic tools is low, histology is the most reliable means to grade the severity of the disease and thus estimate prognosis. Biopsy is also helpful in ruling out an alternative diagnosis. In addition to establishing the cause and severity of disease, histology permits the monitoring of disease progression and the response to therapy, because aminotransaminase levels can decrease during the course of the disease regardless of whether fibrosis progresses or improves.

STAGING FIBROSIS OF NASH

Stage	***Histologic description***
0	No fibrosis
1	Zone 3 perisinusoidal fibrosis only
2	Zone 3 plus portal/periportal fibrosis
3	As above with bridging fibrosis
4	Cirrhosis

Adapted from Brunt *et al.* [28]

NASH ACTIVITY GRADE

Grade	***Steatosis***	***Ballooning***	***Inflammation***
Mild, Grade 1	1–2 (up to 33%)	Minimal	L:1–2 P: none-mild
Moderate, Grade 2	2–3(>33%-66%)	Present	L:2 P:mild-moderate
Severe, Grade 3	3(>66 %)	Marked	L:3 P:mild-moderate

L=lobular, P=portal.

Adapted from Brunt *et al.* [28]

THERAPY FOR NON ALCOHOLIC FATTY LIVER DISEASES:

There is no proven therapy for NAFLD.Patients with simple steatosis probably need only observation with regard to liver disease ,although associated condition may warrant consideration of probable toxicity of common agents such as antihypertensives, anti lipidemics and anti diabetic medications.For patients with mild inflammation and no fibrosis ,a less aggressive observational approach is required because the prognosis appears to be relatively good. A more directed therapy is required if fibrosis is present at biopsy.

DIETARY WEIGHT LOSS AND EXERCISE:

The most practical and most commonly recommended therapy is exercise, diet and weight loss. Weight loss may be associated with progression of liver diseases, especially if the rate of weight loss is more than 1.6 kg per week.Some studies have shown improvement in liver enzyme values, in histologic findings and degree of steatosis, however fibrosis was not significantly altered.

WEIGHT REDUCTION SURGERY:

Roux en y gastric bypass procedure remains popular weight loss procedure for overweight patients, even though it carries a risk of hepatic decompensation .In patients undergoing sustained weight loss after this procedure, plasma glucose, triglycerides, ALT levels are usually reduced. Liver biopsy showed reduction in degree of steatosis, however fibrosis was not significantly altered.

URSODEOXYCHOLIC ACID AND CYTOPROTECTIVE AGENTS:

Initial studies involving people with NASH have shown that treatment with UDCA can lead to improvements in liver enzymes and to a reduction in the severity of fatty deposits in the liver. The potential benefits of UDCA

may be derived from effects on mitochondrial membrane stability, improvement in blood flow or immune modulation UDCA may possibly decrease the risk of developing gallstones during weight reduction. Further studies are ongoing as to the effects of UDCA on NAFLD.

ANTI HYPERLIPIDEMIC AGENTS:

Clofibrate, a triglyceride-lowering drug, has been tested as a treatment but has not shown to be beneficial. Gemfibrozil, another triglyceride-lowering medication was able to improve liver enzyme elevations in a small group of people with NAFLD, but its effects on liver fat and scarring was not tested. Further study is needed on gemfibrozil.There is less rationale in using HMGCoA reductase however they can be safely prescribed for conventional indications .Importantly there is no evidence that patients with pre existing NAFLD are at increased risk of statin induced idiosyncratic hepatatoxicity or statins associated with higher frequency of hepatic steatosis.

ANTI DIABETIC DRUGS:

Metformin, is an insulin sensitizing agent used extensively to treat DM2. The drug was studied in a small series of NASH patients and showed beneficial effects on transaminases and decreased fatty infiltration in the liver. A larger trial is ongoing.

Thiazolidinediones. Among the thiazolidinediones, troglitazone was the first to be studied in NASH patients, who showed some biochemical improvement;[29] however, troglitazone was subsequently withdrawn due to hepatotoxicity. The potential of two newer types of thiazolidinedione–rosiglitazone and pioglitazone–to treat patients with NASH has since been assessed. Both rosiglitazone and pioglitazone have been shown to improve liver enzyme levels and liver histology.[30-32] Although histologic improvement occurred with pioglitazone treatment, however, a significant reduction in fibrosis was not seen.[31] It also seems that the improvement generated by rosiglitazone and pioglitazone is short lasting, and liver enzyme levels become abnormal again once these medications have been discontinued. There remains concern associated with thiazolidinedione treatment as these drugs do have the potential for toxicity[32] and patients tend to gain weight on treatment. Furthermore, because these studies were conducted with relatively small numbers of individuals and over short time periods, well-controlled clinical trials are needed to establish their efficacy.

ANTIOBESITY MEDICATIONS:

In one study, orlistat (an enteric lipase inhibitor) has been shown to promote weight loss and to reduce aminotransferase levels, with improved liver histology in 9 out of 10 NAFLD patients.[33] Sibutramine (a selective serotonin reuptake inhibitor) has been compared with orlistat;[34] both

treatment groups lost weight and improvements were demonstrated in both liver enzyme levels and in the extent of steatosis visible on ultrasound. Despite these encouraging findings, questions remain as to whether these medications can be tolerated long term by patients and whether sustained weight loss can be achieved.[35]

ANTIOXIDANTS AND NUTRITIONAL SUPPLEMENTS:

One preliminary study has indicated that vitamin E (alpha-tocopherol) supplementation may be a beneficial adjunctive treatment for people with NAFLD, but more research is needed in this area.

Betaine is a precursor of S-adenosyl methionine (SAMe), a derivative of the amino acid methionine. S-AMe is purported to promote the health of the liver. In two studies, some patients who were treated with betaine experienced decreased liver enzyme elevations and a decreased amount of fatty deposits in their livers. The mechanism by which betaine exerts its beneficial effect on the liver, is not clear, but it is believed that it may assist in transporting fat away from the liver. More research is needed in this area.

Certain nutritional deficiencies which are common among people with NAFLD may provide a clue in the search for a successful treatment. Some people who receive intravenous feedings for prolonged periods of time develop fatty liver in addition to a choline deficiency. Correcting the

choline deficiency in these people has been shown to resolve the fatty liver as well. Choline supplementation in people with NAFLD is a promising treatment option, but is one which requires further study.

OTHER MEDICATIONS:

Other medications, such as pentoxifylline (Pentoxil, Trental), probiotics, and angiotensin-converting enzyme inhibitors, have been used in small studies of patients with NASH, with encouraging but inconclusive results.

LIVER TRANSPLANTATION:

In patients with decompensated NAFLD cirrhosis, liver transplantation should be considered. Coexisting conditions (e.g., morbid obesity, severe complications of diabetes, cardiac disease) and fear of intraoperative and post-transplantation complications, may preclude transplantation candidacy in these patients. A thorough pretransplantation evaluation, as well as better weight and metabolic derangement control, may be necessary. Following transplant, most patients have persistent metabolic syndrome, with long-term implications. Moreover, NAFLD has been shown to recur in the liver allograft, with a possible rapid progression to steatohepatitis and cirrhosis.

GLYCOGENIC HEPATOPATHY

Glycogenic hepatopathy results from the pathologic accumulation of excess glycogen within the liver and is most commonly associated with poorly controlled type I diabetes mellitus. Additional patient groups that can be affected by glycogenic hepatopathy include those with type II diabetes mellitus, urea cycle defects, and drug effect. Glycogenic hepatopathy was first described by Mauriac as a part of syndrome including growth retardation, cushingoid habitus and delayed puberty[36].It is now becoming clear that liver defect in Mauriac syndrome can occur without syndromal features in adults with type 1 DM [37]–adult variant Mauriac syndrome.

PATHOGENESIS OF GH:

An essential element in pathophysiology of GH is wide fluctuation in both insulin and glucose levels. High serum glucose levels causes an insulin independent inflow of glucose in hepatocytes where it is rapidly phosphorylated, trapping it in cell.Subsequent treatment of high glucose level with insulin causes the trapped glucose to polymerise to glycogen[38].Glycogen production persist for sometime after insulin have declined.Thus alteration in high glucose and insulin level in poorly controlled DM causes GH.

CLINICAL FEATURE AND LAB INVESTIGATION:

The clinical presentation typically includes varying degrees of hepatomegaly, abdominal pain, and elevated transaminases. Occasionally, the transaminase elevations can be dramatic and reach levels of greater than 10 times the upper limit of normal. The liver shows diffusely pale staining hepatocytes on routine H&E stains and excessive glycogen accumulation on PAS stains. Abundant glycogenated nuclei and megamitochondria can be seen, but there should be little or no inflammation, mild or absent fatty change, and no significant fibrosis.

TREATMENT OF GH:

Treatment consist of improving glycemic control. Adequate control of glucose and insulin level causes complete recovery of clinical, biochemical and histological abnormalities.

HEPATITIS C VIRUS AND TYPE 2 DIABETES MELLITUS:

Hepatitis C virus (HCV), the leading cause of liver disease in the United States, is a known independent predictor of type 2 diabetes, the most common endocrine disease even in patients without cirrhosis[39-40]. HCV is known to have a higher prevalence within diabetic patients. When comparing 176 diabetic patients to 6,172 blood donors matched for recognized risk factors of acquiring HCV, there was a higher prevalence of HCV infection within the diabetic patients (11.5 vs. 2.5%, P<0.001).17 Of the diabetic patients with HCV, 72.3% had abnormally elevated LFTs, compared to 27.7% of diabetic patients without evidence of HCV (P< 0.001)[41]. Post liver and renal transplant increase incidence of diabetes is correlated with HCV infection.

The proposed mechanism of HCV related DM suggest role of viral mediated hepatic and peripheral insulin resistance ,up regulation of TNF alpha production and beta cell dysfunction.Development of DM also depends on hepatic parenchymal damage and fibrosis.

This would suggest that any diabetic patient with elevated LFTs needs screening for HCV.

DIABETIC HEPATOSCLEROSIS

Diabetic hepatosclerosis is recently described as micro vascular disease manifested by increased alkaline phosphatase and deposition of collagen and basement membrane in the perisinusoidal space. Collagenization of space of disse positively correlates with the diabetic microangiopathy. The prevalence and clinical significance of DHS is still unclear.DHS may represent a hepatic form of microvascular disease in DM[42].

DIABETES AND HEPATOCELLULAR CARCINOMA

DM is identified as a risk factor for HCC.DM is shown to increase the risk of HCC by two to four folds even after adjusting for other predisposing factors.In a prospective case control study they have demonstrated DM is associated with more advanced HCC and poor outcome.Diabetes appears to increase the recurrence of HCC after potentially curative therapy regardless of etiology of liver disease[43,44,45,46].

POST TRANSPLANT DIABETES MELLITUS

Incidence post liver transplant DM is reported to be from 4% to 31%.Post transplant DM may be associated with HCV, alcoholic cirrhosis, immunosuppressive medication like cyclosporine, tacrolimus,

corticosteroids. Post transplant morbidity and mortality is increased in patients who developed diabetes[47.48].

STATINS IN TYPE 2 DM PATIENTS WITH ELEVATED TRANSMINASES

High-dose statin therapy is associated with more frequent abnormalities of LFTs, although they are generally still relatively infrequent. In the Treating to New Targets (TNT) trial,[49] patients with clinical cardiovascular disease (CVD) were randomized to 10 or 80 mg of atorvastatin. The incidence of persistent elevation in ALT, AST, or both (defined as two consecutive measurements obtained 4-10 days apart that were more than three times the upper limit of the normal range) was 0.2 and 1.2%, respectively ($P < 0.001$).[49]

Because of large trials such as these, current recommendations from the American College of Physicians suggest that type 2 diabetic patients with other cardiovascular risk factors should take a statin for primary prevention of macrovascular complications. These patients do not need routine monitoring of LFTs while on statins unless they have baseline abnormalities in LFTs, myopathy, or are taking other drugs that could increase their risk of adverse events.[50]

For diabetic patients with baseline transaminases less than three times the upper limit of normal, it is not contraindicated to initiate, continue, or advance statin therapy as long as patients are carefully monitored.[51] The frequency of required monitoring in these patients is under debate. There is also a debate as to whether transaminase elevation in statin therapy even constitutes true hepatoxicity.[51] For diabetic patients over the age of 40 years, and certainly in the setting of multiple cardiovascular risk factors or known CVD, the potential risk of statin therapy from the perspective of hepatotoxicity is far outweighed by the proven benefit from CVD risk reduction.

ORAL DIABETIC AGENTS IN TYPE 2 DIABETES MELLITUS PATIENTS WITH ELEVATED TRANSMINASES

The introduction of the insulin sensitizer troglitazone and subsequent cases of hepatotoxicity led Jick et al.[52] to investigate the baseline risk of liver disease in type 2 diabetic patients on oral agents other than thiazolidinediones.[52]

Lebovitz et al.[53] studied more than 6,000 patients with type 2 diabetes in a double-blind clinical trial using various doses of rosiglitazone, placebo, and either glyburide, metformin, or insulin. Mean HBA1C levels at the start of the study were similar across all groups (8.5-9%). Measurement of liver

enzymes occurred at screening, baseline, then every 4 weeks for the first 3 months of treatment and at 6- to 12-week intervals thereafter. Patients were excluded from the study if they had ALT, AST, or ALP greater than two and a half times the upper limit of normal at screening. This is consistent with current recommendations of when not to use rosiglitazone or pioglitazone.

Of those on rosiglitazone, ~3,800 were monitored for at least 6 months, 2,800 for at least 1 year, and 1,000 for at least 2 years. No evidence of hepatotoxic effects were observed in the 5,006 patients who took rosiglitazone. The percentage of patients who developed ALT greater than three times the upper limit of normal were 0.32% of the rosiglitazone group, 0.17% of the placebo group, and 0.40% for the group taking either sulfonylurea, metformin, or insulin. The respective incidence rates of 0.29, 0.59, and 0.64/100 person-years show no difference between treatment of rosiglitazone, placebo, and other antihyperglycemic agents and the development of ALT levels greater than three times the upper limit of normal. Furthermore, of the 5.6% of the patients whose serum ALT values were between one and two and a half times the upper limit of normal at baseline, 66% of those treated with antihyperglycemic medicines normalized their ALTs, whereas only 38.7% of those treated with placebo normalized ALT levels.[53] This supports the important link among glycemic

control, insulin resistance, and hepatic function and suggests that improved glycemic control and improvement in insulin resistance can reduce mild chronic elevation of transaminases often found in diabetic patients. The decrease in LFTs demonstrated with rosiglitazone and pioglitazone therapy in diabetic patients has also been shown in pilot studies using thiadolidinediones to treat NASH, a surrogate for insulin resistance.

CAN ELEVATED LFTs PREDICT THE DEVELOPMENT OF DIABETES MELLITUS?

GGT is a nonspecific marker that is known to rise in patients with type 2 diabetes. In epidemiological studies, it has a positive association with alcohol intake, cigarette smoking, coronary heart disease, BMI, systolic blood pressure, serum triglyceride, heart rate, uric acid, and hematocrit. It has an inverse association with physical activity level.[54] Because GGT increases in diabetes, and increases as BMI increases, it has been proposed as another marker of insulin resistance.

To determine whether elevated GGT could predict the development of type 2 diabetes, a prospective cohort study of 7,458 nondiabetic men aged 40-59 years was conducted for 12 years.[55] Mean serum GGT at the start of the study was significantly higher in the 194 men who developed type 2 diabetes than in the rest of the cohort who did not develop diabetes

(20.9 vs. 15.3 units/l, $P < 0.0001$). The association was independent of serum glucose and BMI.

Ohlson et al.[56] found elevated ALT in nondiabetic Swedish men to be a risk factor for type 2 diabetes, independent of obesity, body fat distribution, plasma glucose, lipid, AST, bilirubin concentrations, and family history of diabetes.

With similar results, Vozaroza et al.[57] followed 451 nondiabetic Pima Indians for an average of 6.9 years to determine whether hepatic enzyme elevations could be linked to the development of type 2 diabetes. At baseline, ALT, AST, and GGT were related to percent body fat. After adjustment for age, sex, body fat, whole body insulin sensitivity, and acute insulin response, only elevated ALT at baseline was associated with an increase in hepatic glucose output. Prospectively, increasing ALT concentrations were associated with a decline in hepatic insulin sensitivity and risk of type 2 diabetes.

The authors concluded that higher ALT is a risk factor for type 2 diabetes and indicates a potential role of increased hepatic gluconeogenesis and/or inflammation in the pathogenesis of type 2 diabetes.

MATERIALS AND METHODS

The study was conducted in Government Royapettah hospital between January 2009 to June 2010. It was a cross sectional study in which patients were interviewed and their data were recorded in a standardized proforma. Data collected included age, gender, duration of diabetes, drug history and co-morbid conditions like hypertension and coronary heart diseases etc. Patients were asked for history of alcohol consumption and the medications used, mainly hepatotoxic drugs as steroids, antiepileptics, amiodarone and antineoplastic drugs. The study was approved by the Ethics Committee and written informed consent obtained from all participants.

The following are the patients inclusion and exclusion criterias.

INCLUSION CRITERIA:

Presence of type 2 diabetes mellitus of any duration.

EXCLUSION CRITERIA:

1. Consumption of alcohol.
2. Seropositivity of HbsAg and antiHCV antibody.
3. Seropositivity of HIV ELISA.

4. Patient on drugs that are proven to cause steatohepatitis (steroids, amiodarone, oral contraceptive pills, and other estrogen containing preparations).

5. Patients with renal failure.

A total of 160 type 2 diabetic patients who met the inclusion criteria were studied during this period. Both inpatients and outpatients attending diabetology outpatient department were included in the study.

Body weight was taken while the patients barefooted and in light clothing, using a weighing scale with accuracy of ±100 g. Standing height was measured without shoes to the nearest cm with the shoulders in a relaxed position and the arms hanging freely. Body mass index. (BMI) (kg/m^2) was calculated as the ratio of weight (kilograms) to the square of height (meters). Patients' BMI was classified according to WHO classification, as being normal (BMI; 18.5 to 24.9 kg/m^2), overweight (BMI; 25 to 29.9 kg/m^2) or obese (BMI>30 kg/m^2).

Waist circumference and hip circumference was measured in a standing position using non stretchable tailor measuring tape to look for central obesity. Central obesity is defined in men by a waist-to-hip circumference ratio greater than 1.0 or a waist circumference greater than 40 inches (102 centimeters). In women, central obesity is defined by a waist-to-

hip ratio greater than 0.8 or a waist circumference greater than 35inches (88 centimeters).

All the above patients were examined and screened for HbsAg, antiHCV antibody, HIV ELISA and were found to be negative. Morning samples of venous blood were collected from patients after fasting for at least 14 hours and tested for glucose, urea, creatinine (using semi auto analyzer Merck 300), hemoglobin A1C (HbA1C) [Using High Performance Liquid Chromatography method], for the liver enzymes; ALT and AST [Using semi auto analyzer Merck 300], and for lipid profile including total cholesterol (TC), high density lipoprotein (HDL), triglycerides (TGL), and low density lipoprotein (LDL)[Using semi auto analyzer Merck 300] and serum protein, albumin, globulin(Using calorimetry photochem -5). Elevated ALT and AST levels were defined as enzyme activity >40 U/L respectively, according to the clinical assay adopted by the center's laboratory..

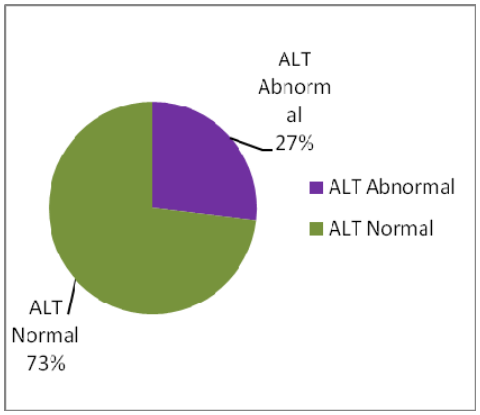
Ultrasound abdomen was done for all patients, to look for size of the liver, echogenecity of liver parenchyma, any evidence of chronic liver disease like coarse echotexture of liver, dilated portal vein and/or splenomegaly. The diagnosis of fatty liver was based on a diffuse hyperechoic echotexture (bright liver) and increased liver echotexture compared with the kidneys.

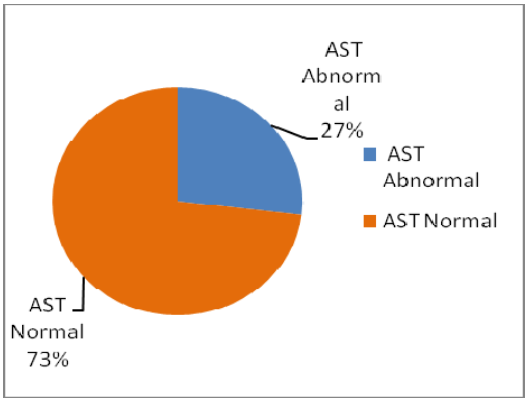
Statistical analysis:

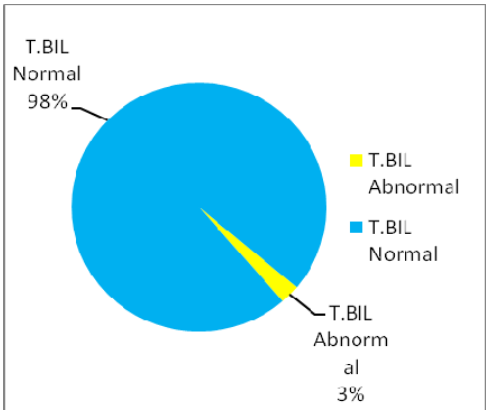
Data analysis was performed using the Statistical Package for Social Sciences (SPSS). The chi-square (χ^2) test was used to determine the association of elevated ALT and AST levels with different variables. A two-tailed *P* value of 0.05 was considered statistically significant.

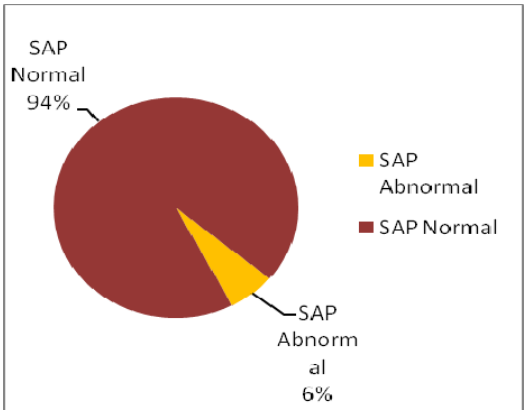
RESULTS

A total of 160 type 2 DM patients (male =65 pts and female =95 pts) who met the inclusion criteria were studied during the study period. Of these 160 patients Serum ALT and AST was found to be elevated in 43 patients(27%), Serum alkaline phosphatase was found to be elevated in 10 patients (6%), Serum bilirubin was found to be elevated in 4 patients (3%).









There was no significant alteration in serum protein or albumin globulin ratio.

1. AGE DISTRIBUTION OF ABNORMAL ALT & AST:

TABLE NO: 1

	ALT & AST	
Age Group	**Abnormal**	**Normal**
30-40 yrs	0 (0%)	7 (100%)
41-50 yrs	15 (31%)	33 (69%)
51-60 yrs	23 (33%)	46 (67%)
61-70 yrs	5 (15%)	28 (85%)
71-80 yrs	0 (0%)	3 (100%)

The mean age of patients with abnormal ALT and AST was 53.23 yrs.

2. SEX DISTRIBUTION OF ABNORMAL ALT & AST:

TABLE NO:2

	ALT & AST	
Gender	**Abnormal**	**Normal**
Female	25 (26%)	70 (74%)
Male	18 (28%)	47 (72%)

The abnormal ALT and AST was seen in 26% of females and 28% of males.

3. BODY MASS INDEX DISTRIBUTION:

TABLE NO: 3

BMI	**ALT & AST**		
	Abnormal	**Normal**	**Pearson Chi square test of significance P value= 0.000**
Underweight	0 (0%)	2 (100%)	
Normal	1 (2%)	59 (98%)	
Over weight	22 (36%)	39 (64%)	
Obese	20 (54%)	17 (46%)	

The abnormal ALT and AST was seen in 36% of overweight patients and 54% of obese patients (p value =0.000).The mean BMI in patients with abnormal ALT and AST was 29.64

4. WAIST HIP RATIO DISTRIBUTION:

In total of 18 males who had elevated transaminases, 14 (77 %) of them had waist hip ratio >1. In total of 25 females who had elevated transaminases, 25(100%) of them had waist hip ratio >0.8.Thus the patients with abnormal ALT & AST was significantly associated with central obesity (p value 0.000).

5. SERUM CHOLESTEROL DISTRIBUTION:

TABLE NO: 5

	ALT & AST		Pearson chi square Test of significance P value =0.011
TOTAL CHOLESTEROL	**Abnormal**	**Normal**	
TOTAL CHOLESTEROL <200	20 (20%)	80 (80%)	
TOTAL CHOLESTEROL >=200	23 (38%)	37 (62%)	

The elevated ALT & AST was common in 38% patients with serum cholesterol >200mg/dl, and it was statistically significant

(p value=0.01).

6. SERUM TRIGLYCERIDES DISTRIBUTION:

TABLE NO: 6

	ALT & AST		Pearson chi square test of significance P value =0.001
TRIGLYCERIDES	**Abnormal**	**Normal**	
TRIGLYCERIDES >=180	33 (38%)	54 (62%)	
TRIGLYCERIDES <180	11 (04%)	63 (86%)	

The elevated transminases was more common in patients with serum triglyceride >180 mg/dl(p value =0.001).

7. In our study we found that 58 % of patients with abnormal ALT and AST was found to have low HDL<40 mg/dl which was found to be statistically insignificant (p value =0.22).

8. The patients with abnormal ALT and AST was found to have poor glycemic control as evidenced by HBA1C. 88% of patient with abnormal ALT and AST have HBA1C >7%. Mean HBA1C in patients with abnormal ALT and AST was 9.98% (p value =0.002).

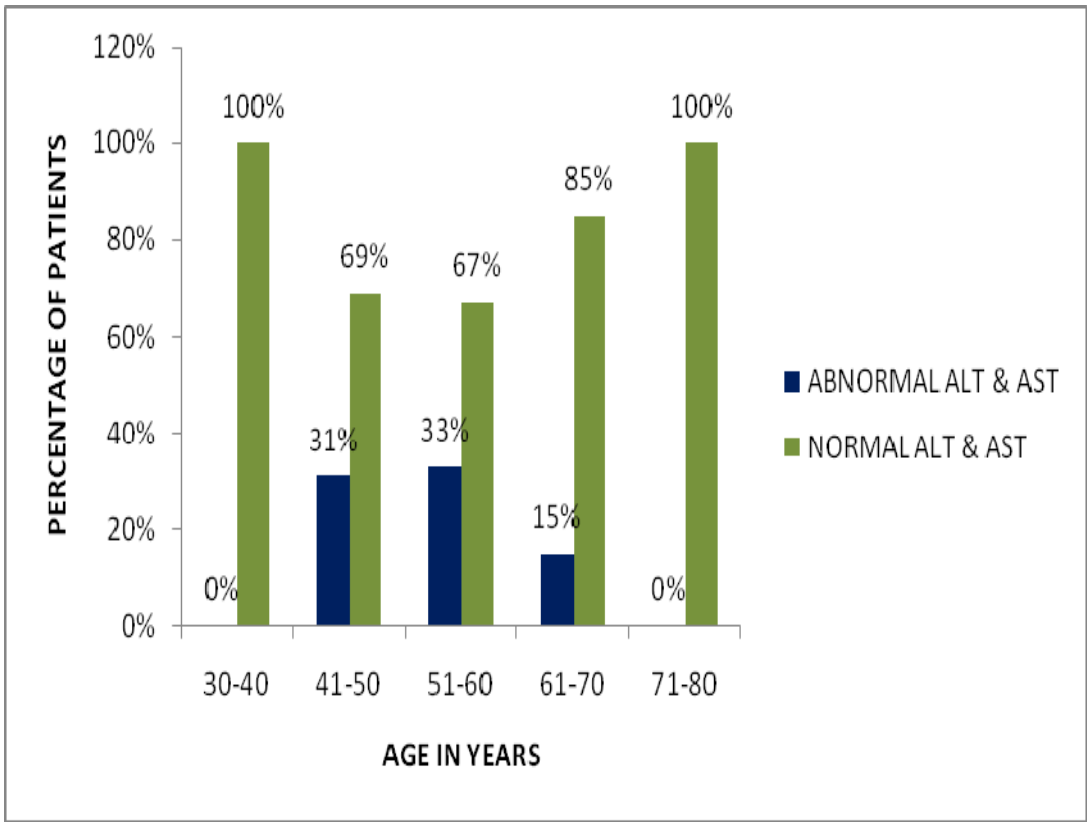
9. The mean duration of diabetes in patients with abnormal ALT and AST was 6.35yrs.

10. Generally in NAFLD the ratio of AST to ALT is less than 1, but this ratio increases as fibrosis advances. In our study AST/ALT ratio <1 was seen in 31 patients(72%) and AST/ALT ratio >1 seen in 12 patients(28%).

11. In our study we have noticed that 72(46%) patients with type 2 DM has USG evidence of fatty liver. Of this 72 patients 44% patients have normal ALT and AST and 56% had abnormal ALT and AST..

CHART 1:

AGE DISTRIBUTION

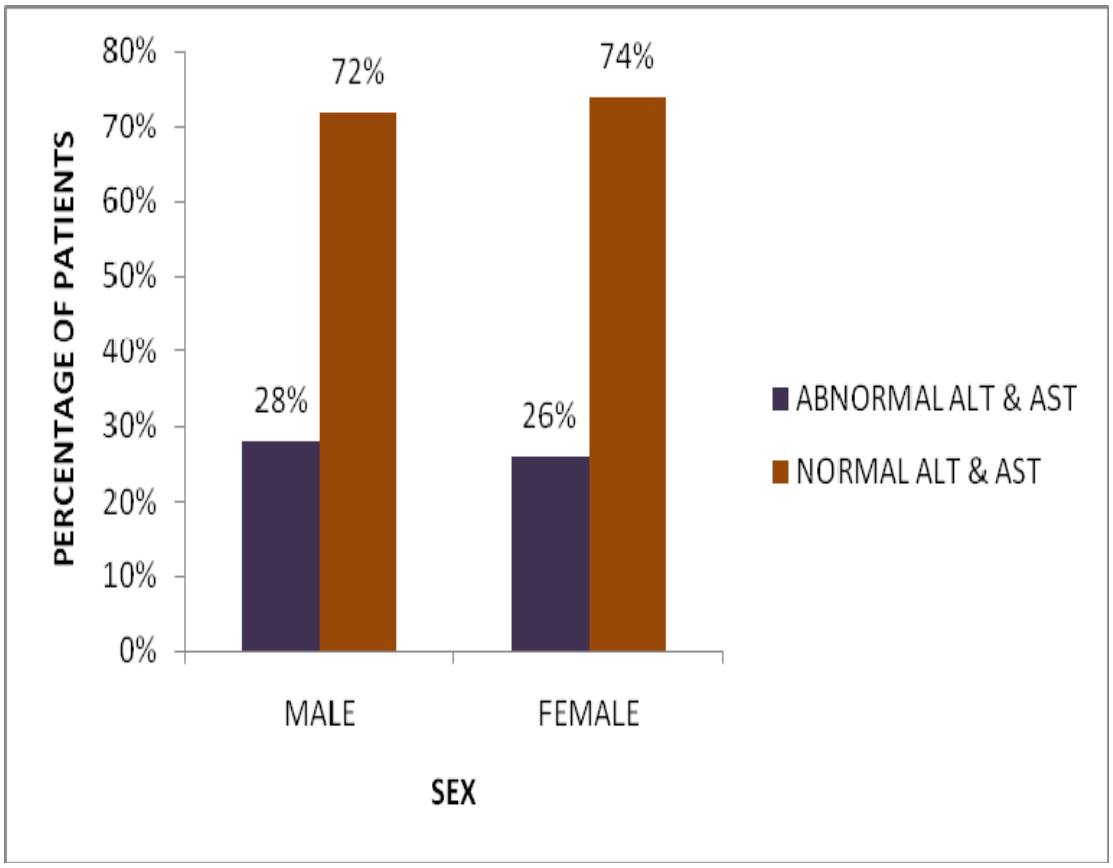


Total no patients =160; mean age of abnormal ALT & AST =53.23yrs

CHART 2:

SEX DISTRIBUTION

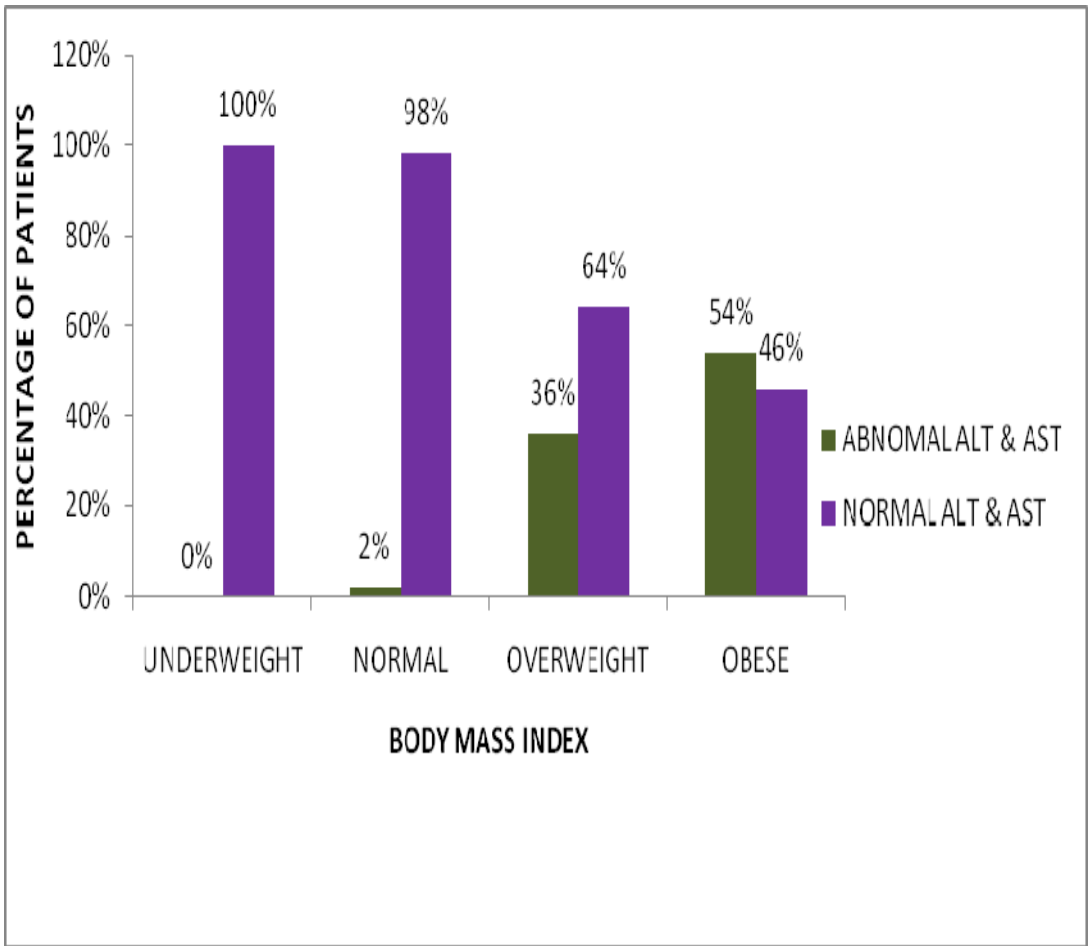
.



Total no of patients =160;

CHART 3:

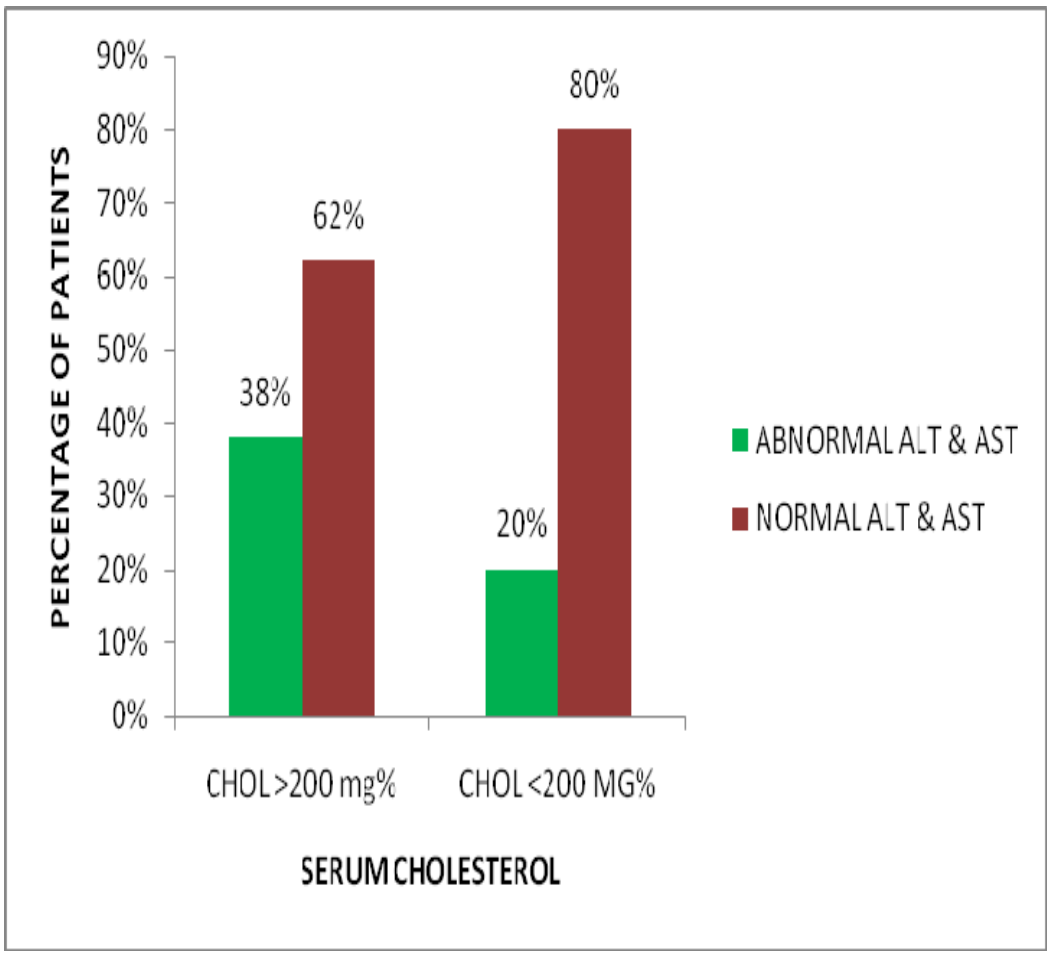
RELATIONSHIP BETWEEN BODY MASS INDEX AND ALT & AST LEVELS



Total no of patients=160; p value = 0.000

CHART 4:

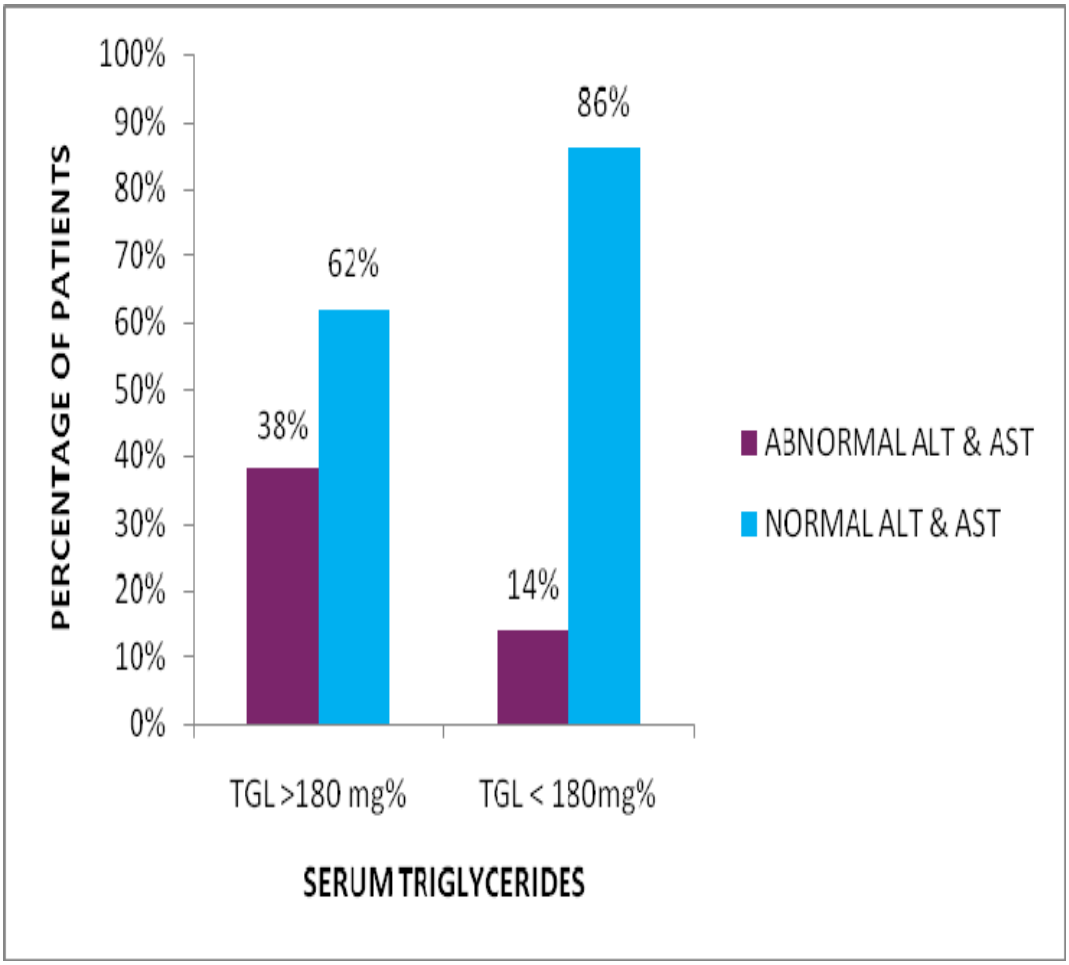
RELATIONSHIP BETWEEN SERUM CHOLESTEROL AND ALT & AST LEVELS



Total no of patients =160; p value = 0.011

CHART 5:

RELATIONSHIP BETWEEN SERUM TRIGLYCERIDES AND ALT & AST LEVELS



Total no of patients =160; p value =0.001

DISCUSSION

Because the liver plays a critical role in the maintenance of carbohydrate homeostasis, glucoregulation, and insulin degradation, it is not surprising that its functions may be affected as a result of diabetes mellitus [58]. Elevated activities of serum aminotransferases are a common sign of liver disease and are observed more frequently among diabetics than in the general population[58].

The prevalence of elevated transaminases levels in type 2 diabetes mellitus is not well known in the Indian population. In earlier studies, applying different methodology and enrolling variable population sample sizes as well as considering different cut-off values for ALT readings has yielded variable prevalence rates[59,60,61,62].

In our present study, prevalence of elevated ALT & AST was found in 27% of patients, elevated ALP was seen in 6% of patients and raised serum bilirubin in 3% of patients. There was no significant alteration in serum protein or albumin globulin ratio.

According to a previous study conducted by Salmela et al [59], in type 2 DM prevalence of abnormal transaminases was found to be 22.9% and raised serum bilirubin is 10.2% . Furthermore in a study conducted by

Sheriff Gonem et al[63] in type 2 DM, reported a lower rate of prevalence of abnormal transaminases which was found to be 15.7%, raised ALP seen in 10%, raised serum bilirubin in 3% individuals.

In our study, elevated transaminases was seen 31% of patients in the age group of 41-50 yrs, 33% in the age group of 51-60 yrs and 15 % in the age group of 61-70 yrs. Supported by earlier studies,[64,65] this finding suggested that severe steatosis denoted by a higher release of the ALT enzyme in response to hepatocytes derangement, tends to occur earlier in the disease process. As a marker of hepatocyte integrity the ALT activity decreases as steatosis progresses. In our study the mean duration of diabetes in patients with abnormal transaminases is 6.34 yrs which was consistent with finding of Salmela et al[59] and Layla Judi et a l[67]. The prevalence of elevated transaminases level decreased with increased age and increased duration of diabetes.

In our study elevated transaminases seen in 28% males and 26% females. However in our study we are not able to demonstrate significant sex difference in prevalence of abnormal transaminases, Erbey et al.[60] reported prevalence rates of 10.7% and 5.3% in type 2 diabetic men and women respectively and West et al.[66] reported a rate of 12.1%; 14.4% in men and 9.3% in women with type 2 diabetes mellitus. Erbey et al [60] and West et al [66] have demonstrated that male gender is a independent predictor

of abnormal ALT levels which was also supported by Layla Judi[67] et al in their study.

In our study we have noticed that elevated transaminases was seen in 36% of overweight category patient and 54% of obese category patients (p value =0.000). These findings are consistent with previous large scale studies by Salmela et al [59] and Erbey et al [60] who reported that prevalence of abnormal transaminases was common in patients with BMI >25 kg/m^2 .

Also in our study the patients with elevated transaminases was significantly associated with central obesity (p value 0.000) which was consistent with study conducted by Layla Judi et al[67]. This finding can be attributed to the fact that elevated ALT levels are more related to central fat distribution than to general obesity. The most obvious explanation for this is that in the presence of insulin resistance, the larger mass of adipose tissue in abdominally obese subjects causes an inappropriate suppression of lipolysis and increased flux of non-esterified free fatty acid from visceral fat to liver. Hence, there is an increase in the size of hepatic free fatty acid pool which favours the accumulation of triglycerides in the hepatocytes. The triglyceride overload provides abundant amounts of substrate for non-oxidative pathways, in addition to causing mitochondrial dysfunction. These lipid-induced changes are believed to ultimately lead to cell apoptosis. [68,69]

In our study patients we noticed that patients with elevated transaminases had a poor glycemic control as evidenced by HbA1C. Mean HBA1C in patients with elevated transaminases was 9.98 (p value =0.002), which was consistent with finding of Salmela et al[59] who demonstrated a mean HBA1C OF 11.2% in patients with elevated transaminases indicating poor glycemic control.

We have also observed like other people that raised transaminases is closely related to other features of metabolic syndrome in addition to type 2 diabetes [70], like obesity and serum triglycerides more than180 mg/dl. 38% of our patients had a fasting serum triglycerides level of more than 180 mg/dl which was found to be statistically significant (p value=0.001). Our results are consistent with findings of Shahid ahmed et al[71] who reported 42.6% patients with elevated transaminases had serum triglycerides >180 mg/dl.

In our study we found that 58 % of patients with abnormal ALT and AST was found to have HDL<40 mg/dl which was found to be statistically insignificant (p value =0.22) which is consistent with finding of Layla Judi et al.

In our study we found that elevated ALT & AST was common in patients with serum cholesterol >200mg/dl, and it was statistically

significant (p value=0.011) which was not consistent with finding of Shahid ahmed et al[71] who reported that association of serum cholesterol and abnormal transaminases is statistically insignificant.

All patients with elevated transaminases showed fatty liver on ultrasound and Though we did not do liver biopsies in these patients, ultrasonographic appearance of fatty liver has a good predictive value for NAFLD. It has already been established that mild to moderate elevation of serum aminotransferases is the most common laboratory abnormality in patients with non alcoholic fatty liver disease (NAFLD). NAFLD is the commonest cause of elevated aminotransferases in type 2 diabetic patients, and our study confirms that too. In the United States, NAFLD is replacing alcohol and viral hepatitis as the most common aetiology of chronically elevated LFTs, in both diabetic and non diabetic individuals.

Since all our patients included in our study were on Oral hypoglycaemic agents (metformin and sulphonylureas) ,we are not able to substantiate the difference in the prevalence of abnormal transaminases in insulin and OHA groups. The spectrum of NAFLD, including its severe form NASH, has been consistently associated with insulin resistance and hyperinsulinaemia[72-74]. This has raised a concern that treatment with insulin in type 2 diabetes may aggravate liver disease. Consistent with this, in data from de Marco et al[75]., the standardized mortality ratio from cirrhosis in

patients with type 2 diabetes was higher in those treated with insulin (OR 6.8 vs. diet alone) than in those on oral hypoglycaemic agents (OR 4.9 vs. diet alone).[75] However, both hyperglycaemia and hyperinsulinaemia can promote fatty infiltration of the liver. Long-standing type 2 diabetes may be associated with relative insulin deficiency, and appropriate insulin treatment would shift the balance against hepatic steatosis. However previous study conducted by West et al[66] and Salmela et al[59], shows that insulin use may be protective against the effects of elevated ALT levels. Although this finding suggests that administration of insulin to diabetic patients may help to avoid harmful involvement of the liver by inflammation and fibrosis, it requires further investigation.

Our study has limitations. Firstly, the prevalences of raised transaminases may still be underestimates. A single estimation of ALT was used to define abnormality. Fluctuation in the ALT levels is recognized in patients with chronic liver disease, and a single measurement can underestimate disease burden[76]. Secondly,Since all our patients were on oral hypoglycaemic agents, we are not able to substantiate the difference in the prevalence of abnormal transaminases in insulin and OHA groups.Thirdly, In our study we didn't do a liver biopsy as most of the patients being asymptotatic denied consent for invasive procedure. Lastly, as the study included patients attending their hospital review, there is likely to be some

selection bias. A variety of factors including referral pattern and poor control can influence the selection of patients for regular hospital review. Although we have controlled for this to some extent by including HBA1C in our analysis, findings of current study well required confirmation in population based studies.

SUMMARY

- In our present study, prevalence of elevated ALT & AST was found in 27% of patients, elevated ALP was seen in 6% of patients and raised serum bilirubin in 3% of patients. There was no significant alteration in serum protein or albumin globulin ratio.

- The prevalence of abnormal transaminases in type 2 DM decreases with increasing age i.e: more common in younger age group and also decreases with increase in duration of diabetes.

- Though we are not able to demonstrate significant sex difference in prevalence of abnormal transaminases, previous studies have demonstrated that male gender is a independent predictor of abnormal ALT levels

- The prevalence of abnormal transaminases was more common in patients with BMI > 25 kg/m^2 and also in patients with central obesity.

- The patients with abnormal transaminases was found to have poor glycemic control as evidenced by HBA1C.

- We have also observed like other people that raised transaminases is closely related to other features of metabolic syndrome in addition to type 2 diabetes , like obesity and serum triglycerides more than180 mg/dl.

- All patients with elevated transaminases showed fatty liver on ultrasound.

- NAFLD is the commonest cause of elevated aminotransferases in type 2 diabetic patients, and our study confirms that too.

- These findings necessitate interference by lifestyle modification and early therapeutic measures to control risk factors, especially obesity, in younger diabetics which might help to prevent chronic liver disease.

CONCLUSION

A high proportion of patients with diabetes mellitus in our catchment population have abnormal liver function tests that may be a marker for NASH and insulin resistance. Currently, routine liver function screening is not being advocated in type 2 diabetics but emerging evidence suggests that abnormal LFT may be a marker for metabolic syndrome and insulin resistance in type 2 diabetes. Such patients would thus warrant more intensive metabolic control particularly of their hyperglycaemia and dyslipidaemia and also their obesity and hypertension to not only reduce cardiovascular risk attributed to by their insulin resistance but also to prevent progression to significant hepatic dysfunction like cirrhosis and hepato-cellular carcinoma.

BIBLIOGRAPHY

1. Definition and diagnosis of diabetes mellitus & intermediate hyperglycemia.Report of WHO/IDF consultation 2006.

2. Yoon KH, lee JH, Choi YH, Ko SH, Zimmet T, Son Y. Epidemic obesity and type 2 DM in Asia.Lancet 2006;368:1681-88.

3. Trombetta M, Spiazzi G.Type 2 DM and chronic liver disease in Verona diabetes study.Alim pharm ther 2005:22:24-7.

4. Holder A,Der Diabetes mellitus In: Nothangels Hnadbuch.Wien A,holder 1906.

5. Adami HO, Chow WH, Nyrén O, Berne C, Linet MS, Ekbom A, et al. Excess risk of primary liver cancer in patients with diabetes mellitus. J Natl Cancer Inst 1996;88:1472-7.

6. Caldwell SH, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: Clinical charecterization and risk factors for underlying disease. Hepatology 1999;29:664-9.

7. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002;346:1221-31.

8. Rosen F, Roberts NR, Nichol CA. Glucocorticosteroids and transaminase activity: Increased activity of glutamic pyruvic transaminase in four conditions associated with gluconeogenesis. J Biol Chem 1959;476:80.

9. Westerbacka J, Cornér A, Tiikkainen M, Tamminen M, Vehkavaara S, Häkkinen AM, et al. Women and men have similar amounts of liver and intraabdominal fat, despite more subcutaneous fat in women: Implications of sex differences in markers of cardiovascular risks.Diabetologia 2004;47:1360-9.

10. Kim HC, Jee SH, Han KH. Normal serum aminotransferase concentration and risk of mortality from liver disease: Prospective cohort study. Br Med J 2004;328:983-7.

11. Ioannou GN, Weiss NS, Boyko EJ, Mozaffarian D, Lee SP. Elevated serum alanine aminotransferase activity and calculated risk of coronary heart disease in the United States. Hepatology 2006;43:1145-51.

12. DeRosa G, Swick RW. Metabolic implications of the distribution of the alanine aminotransferase isoenzymes. J Biol Chem 1975;250:7961-7.

13. Clark JM, Diehl AM. Defining non-alcoholic fatty liver disease: Implications for epidemiological studies. Gastroenterology 2003;124:248-50.

14. Lewis GF, Carpentier A, Khosrow A, Giacca A: Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. Endocr Rev 23: 201-229,2002 .

15. Shimomura I, Matsuda M, Hammer RE, Bashmakov Y, Brown MS, Goldstein JL: Decreased IRS-2 and increased SREBP-1c lead to mixed insulin resistance and sensitivity in livers of lipodystrophic and ab/ab mice. Mol Cell6: 77-86,2000 .

16. Neuschwander-TetriBA, Caldwell S: Nonalcoholic steatohepatitis: summary of AASLD single topic conference. Hepatology37: 1202-1219,2003 .

17. Grove J, Daly AK, Bassendine MF, Day CP: Association of a tumor necrosis factor promoter polymorphism with susceptibility to alcoholic steatohepatitis. Hepatology 26:143 -146, 1997.

18. O'Brien RM, Granner DK: Regulation of gene expression by insulin. Biochem J 278: 609-619,1991

19. Baig N, Herrine S Rubin R. Liver diseases and diabetes mellitus.Clin Lab Med 2001;21:193-207.

20. El–serag HB, Tran T, Everhar T Diabetes increase the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology 2004;126:460-68.

21. Matteoni CA, Younossi ZM,Gramlich T,Boparai N Chang Liu Y,Mc Cullough AJ.NAFLD :A spectrum of clinical and pathological severity Gastroenterology 1999;116:1413-19.

22. Marchesini G, Bugianesi E,Forlani G et al NAFLD .Steatohepatitis and metabolic syndrome.Hepatology 2003;37:917-23.

23. P.Vuppalanchi &N Chalasani. NAFLD AND NASH: Selected practical issues in their evaluation and management.Hepatology 2009;49:306.

24. Day CP, James OF Steatohepatitis: a tale of two 'hits'? Gastroenterology 1998;114:842-5.

25. Baranova A, Younossi ZM. Adipokines in non-alcoholic fatty liver diseases. *Adipose Tissue and Adipokines in Health and Disease,* 1st edn. The Humana Press, Totowa, NJ 2006:291-305.-317.

26. Satapathy SK, Garg S, Chauhan R, *et al*. Beneficial effects of tumor necrosis factor-alpha inhibition by pentoxifylline on clinical, biochemical, and metabolic parameters of patients with nonalcoholic

steatohepatitis.*Am J Gastroenterol* 2004; 99: 1946-52.

27. Steppan CM, Bailey ST, Bhat S, *et al.* The hormone resistin links obesity to diabetes. *Nature* 2001; 409: 307-12

28. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander –Teri BA, Bacon BR, NASH a proposal for staging and grading histological lesion.AM J Gastroenterology 1999;94:2467-74.

29. Caldwell SH, Hespenheide EE, Redick JA, Iezzoni JC, Battle EH, Sheppard BL. A pilot study of a thiazolidinedione, troglitazone, in nonalcoholic steatohepatitis. *Am J Gastroenterol* 2001; 96: 519-25.

30. Iwata M, Haruta T, Usui I, *et al.* Pioglitazone ameliorates tumor necrosis factor-alpha-induced insulin resistance by a mechanism independent of adipogenic activity of peroxisome proliferator-activated receptor-gamma.*Diabetes* 2001; 50: 1083-92.

31. Bajaj M, Suraamornkul S, Hardies LJ, Pratipanawatr T, DeFronzo RA. Plasma resistin concentration, hepatic fat content, and hepatic and peripheral insulin resistance in pioglitazone-treated type II diabetic patients. *Int J Obes Relat Metab Disord* 2004; 28: 783-9.

32. Jung HS, Youn BS, Cho YM, *et al.* The effects of rosiglitazone and metformin on the plasma concentrations of resistin in patients with type 2 diabetes mellitus. *Metabolism* 2005; 54: 314-20.

33. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care.* 2004;27:155-161.

34. Sabuncu T, Nazligul Y, Karaoglanoglu M, *et al*. The effects of sibutramine and orlistat on the ultrasonographic findings, insulin resistance and liver enzyme levels in obese patients with non-alcoholic steatohepatitis. *Rom J Gastroenterol* 2003; 98: 926-30.

35. Brolin RE. Bariatric surgery and long-term control of morbid obesity. *JAMA* 2002; 288: 2793-6.

36. Mauriac P cros ventre hepatomegalie,troubles de las groissance chez les enfants diabetiales traits depuis plesleurs annes par L insulin gaz hebd med Bordeaux 1930;26:402-10.

37. Chatlia R, West AB.Hepatomegaly and abnormal liver function test in adults with diabetes 1996;75:327-33

38. N Ferrer JC,farre C,Gomis RR et al.control of glycogen deposition ,FEBS 2003;540:127-32

39. Baig NA, Herrine SK, Rubin R: Liver disease and diabetes mellitus. Clin Lab Med 21: 193-207,2001

40. Knobler H, Schihmanter R, Zifroni A, Finakel G, Schattner A: Increased risk of type 2 diabetes in noncirrhotic patients with chronic hepatitis C virus infection. Mayo Clin Proc 75:355 -359, 2000.

41. Simo R, Hernandez C, Genesca J, Jardi R, Mesa J: High prevalence of hepatitis C virus infection in diabetic patients. Diabetes Care19 : 998-1000, 1996.

42. Chen G, Brunt EM,Diabetic hepatosclerosis : a 10 yr autopsy series. Liver international 2009;29:1044-1050.

43. Lia M,Hsieh M,Chur Chen T, Type 2 DM and HCC: A cohort study in high prevalence area of hepatitis virus infection.Hepatol 2006;43:6:1295-1302.

44. Caldwell SH,OLIVERIA CPMS,de Lima VMR,Park SH.NASH, cryptogenic cirrhosis and HCC.CHAPTER IN INTERNATIONAL UPDATES ON HEPATOLOGY,Ed Ramon Batallar,permanyer publication 2007.

45. Caldwell SH,Crespo DM Kang HS AL –Qsaimi AM.Obesity and HCC.Gastroenterology 2004;127:97-103.

46. Qian Y and Fan JG.Obesity ,fatty liver and liver cancer.hepato biliary pancreat dis int 2005;4:173-77.

47. Tueche SG,Diabetes after liver transplant new etiological clues and corner stone for understanding transplant proc 2003;35:1466-1468.

48. John PR,Thuluvath PJ.Outcome of patients with new onset diabetes after liver transplantation compared with those without diabetes liver transpl 2002;8:708-713.

49. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK, the Treating to New Targets (TNT) Investigators: Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 352:1425 -1435, 2005.

50. Snow V, Aronson M, Hornbake R, Mottur-Pilson C, Weiss K: Lipid control in the management of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med140: 644-650, 2004.

51. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C, for the American College of Cardiology, American Heart Association and National Heart, Lung and Blood Institute: ACC/AHA/NHLBI clinical advisory on the use and safety of statins. Stroke 33:2337 -2341, 2002 .

52. Jick SS, Stender M, Myers M: Frequency of liver disease in type 2 diabetic patients treated with oral antidiabetic agents. Diabetes Care22: 2067-2071,1999.

53. Lebovitz H, Kreider M, Freed M: Evaluation of liver function in type 2 diabetic patients during clinical trials: evidence that rosiglitazone does not cause hepatic dysfunction. Diabetes Care 25:815 -821, 2002.

54. Wannamethee G, Ebrahim S, Shaper AG: Gamma-glutamyltransferase: determinants and associations with mortality from ischaemic heart disease and all causes. Am J Epidemiol 42:699 -708, 1995

55. Perry IJ, Wannamethee SG, Shaper AG: Prospective study of serum gamma-glutamyltransferase and risk of NIDDM. Diabetes Care 21: 732-737,1998.

56. Ohlson LO, Larsson B, Bjorntorp P, Erksson H, Svardsudd K, Welin L, Tibblin G, Wilhelmsen L: Risk factors for type 2 diabetes mellitus:

thirteen and one-half years of follow-up of the participants in a study of Swedish men born in 1913. Diabetologia 31:798 -305, 1988

57. Vozarova B, Stefan N, Lindsay RS, Saremi A, Pratley RE, Bogardus C, Tataranni PA: High alanine aminotransferases is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. Diabetes51 : 1889-1895,2002

58. Fagiuoli SR, Van Thiel DH. The liver in endocrine disorders. In: Rustgi VK, Van Thiel DH, editors. The liver in systemic disease. New York: Raven Press; 1993. p. 285-301.

59. Salmela PI, Sotaniemi EA, Niemi M, Maentausta O: Liver function tests in diabetic patients. Diabetes Care 7:248 -254, 1984 Abstract

60. Erbey JR, Silberman C, Lydick E: Prevalence of abnormal serum alanine aminotransferase levels in obese patients and patients with type 2 diabetes. Am J Med 109: 588-590,2000

61. Kejariwal D, Phillips M, Dhatariya. Abnormal liver function tests and diabetes mellitus: A secondary care prevalence study. Diabetes Med 2008;25:1-33.

62. Qari F, AlGhamdi A. Fatty liver in overweight and obese patients in western part of Saudi Arabia: A study of sonological prevalence. Pak J Med Sci 2005;21:143-7.

63. Sherif Gonem, Alan wall, Parijat de.Prevalence of abnormal liver function test in Type 2DM.Endocrine abstracts 2007;13:157.

64. Coppack SW, Jensen MD, Miles JM. In vivo regulation of lipolysis in humans. J Lipod Res 1994;35:177-93.

65. Ioannou GN, Boyko EJ, Lee SP. The prevalence and predictors of elevated serum aminotransferases activity in the United States in 1999-2002. Am J Gastroenterol 2006;101:76-82.

66. West J, Brousil J, Gazis A, Jackson L, Mansell P, Bennett A, et al. Elevated serum alanine transaminase in patients with type 1 or type 2 diabetes. Q J Med 2006;99:871-6.

67. Judi L, Toukan A, Khader Y, Ajlouni K, Khatib MA. Prevalence of elevated hepatic transaminases among Jordanian patients with type 2 diabetes mellitus. Ann Saudi Med 2010;30:25-32

68. Marceau P, Biron S, Hould FS, Marceau S, Simard S, Thung SN, et al. Liver pathology and the metabolic syndrome X in severe obesity. J Clin Endocrinol Metab 1999;484:1513-7.

69. Kotronen A, Juurinen L, Hakkarainen A, Westerbacka J, Cornér A, Bergholm R, et al. Liver fat is increased in type 2 diabetic patients and underestimated by serum Alanine Aminotransferase compared

with equally obese non-diabetic subjects. Diabetes Care 2008;31:165-9.

70. Nannipieri M, Gonzales C. Liver enzymes, the metabolic syndrome and incident diabetes. Diabetes Care. 2005; 28: 1757–62.

71. Shahid Ahmed, Nadir Ali, Zafar Abdullah, Mohammad Ilyas, Uzma Naeem,study of raised alanine amino transferase in type 2 dm ,pafmj 2008;3:9.

72. Sanyal AJ, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, Luketic VA, Shiffman ML, Clore JN. (2001) Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. Gastroenterology 120 1183–92.

73. Pagano G, Pacini G, Musso G, Gambino R, Mecca F, Depetris N, Cassader M, David E, Cavallo-Perin P, Rizzetto M. (2002) Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. Hepatology 35 367–72.

74. Chitturi S, Abeygunasekera S, Farrell GC, Holmes-Walker J, Hui JM, Fung C, Karim R, Lin R, Samarasinghe D, Liddle C, Weltman M, George J. (2002) NASH and insulin resistance: insulin hypersecretion

and specific association with the insulin resistance syndrome. Hepatology 35 373–9.

75. De Marco R, Locatelli F, Zoppini G. (1999) Cause-specific mortality in type 2 diabetes. Diabetes Care 22 756–61.

76. Diehl AM and Clark JM. (2003) Defining non-alcoholic fatty liver disease: implications for epidemiological studies. Gastroenterology 124 248–50.

PROFORMA

NAME:

I.P/O.P.NO:

AGE: yrs.

SEX: Male/Female.

OCCUPATION:

ADDRESS:

HEIGHT: cm. WEIGHT: kg. BMI:

WAIST: cm. HIP: cm. WAIST HIP RATIO:

DURATION OF DIABETES MELLITUS:

ON TREATMENT WITH

PRESENCE OF COMORBID ILLNESS:

Hypertension /Coronary heart diseases /chronic kidney diseases /tuberculosis /chronic obstructive pulmonary diseases/cerebrovascular accidents /Epilepsy / chronic liver diseases.

ANYOTHER ILLNESS:

DRUG HISTORY:

PERSONAL HISTORY:

FAMILY HISTORY:

EXAMINATION OF THE PATIENT:

INVESTIGATION:

HBSAg: ANTIHCV: HIV ELISA:

BLOOD SUGAR: HbA1C:

BLOOD UREA: SERUM CREATININE:

LIVER FUNCTION TEST:

SERUM BILIRUBIN: DIRECT: INDIRECT:

AST: ALT: ALP:

SERUM PROTEIN: ALBUMIN: GLOBULIN:

SERUM LIPID PROFILE:

TOTAL CHOLESTEROL:

HDL: LDL: VLDL:

TRIGLYCERIDES:

ULTRASOUND ABDOMEN:

ABBREVIATIONS

DM	–	Diabetes mellitus
NAFLD	–	Non alcoholic fatty liver diseases.
NASH	–	Non alcoholic steatohepatitis
HCV	–	Hepatitis C virus
HCC	–	Hepatocellular carcinoma
GH	–	Glycogenic hepatopathy
DHS	–	Diabetic hepatosclerosis
CVD	–	Cardiovascular disease
CAD	–	Coronary heart diseases
HT	–	Hypertension
COPD	–	Chronic obstructive pulmonary diseases
CVA	–	Cerebrovascular accidents
LFT	–	Liver function tests
ALT	–	Alanine transaminase
AST	–	Aspartate transaminase

ALP	–	Alkaline phosphatase
GGT	–	Gamma glutamyl transferase
T.PRO	–	Total protein
ALB	–	Albumin
GLO	-	Globulin
CHOL	–	Cholesterol
TGL	–	Triglyceride
HDL	–	High density lipoprotein
LDL	–	Low density lipoprotein
VLDL	–	Very low density lipoprotein
USG	–	Ultra sound
HBA1C	–	Glycosylated haemoglobin
BMI	–	Body mass index
WHR	–	Waist hip ratio
HBSAg	–	Hepatitis surface antigen
ANTI HCV	–	Hepatitis C virus antibody

HIV	–	Human immunodeficiency virus
TNF α	–	Tumor necrosis factor α
UDCA	–	Urso deoxycholic acid
SAMe	–	S adenosyl methionine.
MF	–	Metformin
G	–	Glibenclamide
GM	–	Glimepride
GZ	-	Glipizide